

release composition according to the present invention. Specific examples of such usages in the instant claims are as illustrated below:

Claims 1 and 41	"on average no more than about 20% of the pramipexole is dissolved within 2 hours after placement of the composition in a standard dissolution test . . ."
Claims 1 and 8	"the time to reach a mean of 20% absorption is greater than about 2 hours and/or the time to reach a mean of 40% absorption is greater than about 4 hours"
Claim 3	"no more than about 12% . . . dissolves within 1 hour in said test"
Claims 4, 5, 6, 7	"time to reach 50% dissolution is at least about [4 hours, 6 hours, 8 hours, or 12 hours]"
Claim 9, 10	"time to reach a mean of 40% absorption is at least about [5 hours, 6 hours]"
Claim 12	"exhibits a maximum plasma concentration ( $C_{max}$ ) of pramipexole that is not greater than about 0.3 ng/ml"
Claims 13 and 14	"exhibits a time to reach maximum plasma concentration ( $T_{max}$ ) of pramipexole that is at least about [6 hours, 8 hours] following administration of the composition"
Claim 15	"a fluctuation ratio that is not substantially greater than that of an equal daily dose of an immediate-release pramipexole dihydrochloride reference formulation, administered three times a day"

Applicants herein reiterate and incorporate by reference all the arguments presented in the response filed May 12, 2010. As explained therein, a person skilled in the art can readily perform the in vitro dissolution and/or in vivo pharmacokinetic testing protocols following the specific guidance presented in the application in order to obtain the relevant test results to reasonably determine whether they fall within the scope of the claims. As additional guidance, reference can also be made to the in vitro and in vivo pharmacokinetic test results that are disclosed in the instant application for three extended release tablets according to the present invention.

The instant application discloses an extended release tablet formulation functioning to provide extended release within a biological system. The Applicants have found that having a certain dissolution rate at an early time frame in an in-vitro dissolution test is indicative of an acceptable in vivo PK profile for the extended release formulation. See Paragraph [0027], 2<sup>nd</sup> sentence (emphasis added):

*"It is surprisingly found that data for early time points (up to about 2 hours) and/or initial dissolution rates (up to about 20% dissolution) in the in vitro test described herein are*

*indicative of a PK profile consistent with the present invention."*

As a consequence thereof, it was found that the early time frame dissolution data of the extended release formulation comprising pramipexole is an indicator of an acceptable in vivo PK profile/PK data and thus a kind of "surrogate" parameter for predicting an acceptable PK profile.

The instant application also recognizes the fact that the specific PK data/PK profile that is obtained is subject to the usual variation as would be expected from a biological system. See, e.g., Paragraph [0021], 2<sup>nd</sup> sentence:

*"It will be understood that PK data are subject to the usual variation seen in biological data, thus the absorption percentages specified above are means from a population, typically at least about 8 in number, of individual healthy adults in accordance with standard statistical practice."*

This recognizes that PK data is subject to the usual variation between individual patients. It is also well known that PK profiles can vary greatly between different drug substances/drug products.

See Paragraph [0024]:

*"Among drugs used to treat Parkinson's disease, levodopa is a well-known example, having a short elimination half-life ( $T_{1/2}$ ) of about 1.5 hours. See Colosho & De Michele (1999), European Journal of Neurology 6(1), 1-21. By contrast, pramipexole has a  $T_{1/2}$  of about 9 to about 14 hours, depending on the particular study, and would not on this ground be expected to require special attention to formulation to enable once-daily dosing."*

The above evidences that even if exact dissolution and PK data are given, for example as average data, the skilled person in the art knows that the numerical figure described literally is not to be taken as a mathematical absolute but only as a guided lead, since we are dealing, in the end, with a biological system.

Applicants' primary objective was to develop an extended release tablet that will exhibit a PK profile that allows a once-daily administration on one hand and that, on the other hand, is at least comparable to the results achieved with a thrice daily dosing of a standard immediate release tablet formulation of pramipexole. In doing so, Applicants have identified a certain in-vitro dissolution profile that is indicative of an acceptable in vivo PK profile. The language that Applicants have used in the specification clearly indicates a recognition that the numerical end points used for the target dissolution rate and in-vivo profile should not be considered absolute end points and that some variability must be allowed.

See, e.g., Paragraph [0027] (emphasis added):

*"It is surprisingly found that data for early time points (up to about 2 hours) and/or initial dissolution rates (up to about 20% dissolution) in the in vitro test described herein are indicative of a PK profile consistent with the present invention. Thus a pramipexole composition exhibiting no more than about 20% dissolution at a 2 hour time point in the in vitro test is strongly indicative of a desirable in vivo PK profile, whereas one exhibiting faster early dissolution, even if 50% and 80% dissolution times are no different, is not so indicative."*

The usage of the terms "about", "strongly indicative" and "not so indicative" clearly demonstrate that the numerical end points used should not be considered absolute end points and that some variability must be allowed, to account for the fact that we are dealing, in the end, with the effects on a biological system in which absolute predictability is not possible.

For all the above reasons, the Examiner must understand that there is an inherent variability that must be expected in such in-vitro dissolution and in-vivo PK results even though the pharmacokinetic testing is performed using well-defined protocols. As such, it has been commonplace in this field to utilize words of approximation, e.g. "about" and "substantially", when defining such dissolution and PK parameters of pharmaceutical formulations. This commonplace usage is represented by the large number of issued U.S. patents that include such words of approximation when speaking to such dissolution and PK parameters, both in the context of immediate-release and controlled-release formulations as outlined below.

#### **U.S. Patents in the Field Having Terms of Approximation**

Many U.S. patents in the field have issued including claim terms of approximation, e.g. "about" and "substantially", in connection with claiming in-vitro dissolution and in-vivo PK parameters of pharmaceutical formulations. Examples of such patents, and their relevant claim language, are listed in the table below:

Patent Number	Issue Date	Subject Matter	Exemplary Claim Language <sup>1</sup>
7799331	9/21/2010	Oral suspension of prednisolone acetate	Claim 20: the composition exhibits an in vitro dissolution profile of about 85% released after about 15 minutes, about 95% released after about 30 minutes, about 97% released after about 45 minutes and about 97% released after about 60 minutes.

<sup>1</sup> Relevant portions of the claims are provided

7781449	8/24/2010	Once daily dosage forms of trospium	Claim 1: wherein said administration provides steady state blood levels of trospium of a minimum of about 0.5 ng/ml and a maximum of about 6.0 ng/ml
7781448	8/24/2010	Once daily dosage forms of trospium	<p>Claim 1: once-a-day administration provides steady state blood levels of trospium of a minimum of about 0.5 ng/ml and a maximum of about 6.0 ng/ml</p> <p>Claim 16: wherein said DR component releases trospium at a pH of about 7.0.</p> <p>Claim 24: once-a-day administration of said pharmaceutical composition provides steady state blood levels of trospium that are comparable to steady state blood levels of trospium achieved with twice daily administration of 20 mg immediate release (IR) trospium chloride tablets.</p>
7572641	8/11/2009	Pharmaceutical compositions of meloxicam	<p>Claim 1: determining the amount by weight of meloxicam dissolved from the reference meloxicam pharmaceutical formulation and the amount by weight of meloxicam dissolved from the meloxicam pharmaceutical formulation after about 15 minutes from starting the dissolution of each formulation</p> <p>Claim 3: wherein the mean <math>C_{max}</math> is from about 1200 ng/ml to about 1500 ng/ml when dosed at 15 mg to healthy volunteers.</p> <p>Claim 5: wherein the pharmaceutical formulation has a mean <math>AUC_{0-\infty}</math> from about 39000 ng*hr/ml to about 61000 ng*hr/ml when dosed at 15 mg to healthy volunteers.</p> <p>Claim 11: between 60% and 85% by weight of meloxicam dissolves within about 15 minutes after starting dissolution of the pharmaceutical formulation</p> <p>Claim 13: having a mean <math>AUC_{0-\infty}</math> from about 39000 ng*hr/ml to about 61000 ng*hr/ml when dosed at 15 mg to healthy volunteers.</p>
7465462	12/16/2008	Controlled release selective serotonin reuptake inhibitor formulation	Claim 1: wherein the composition allows the controlled release of the fluvoxamine over a period of not less than about 12 hours following oral administration . . . wherein the fluvoxamine release rate from the composition exhibits the following in vitro dissolution pattern when measured using a USP type II dissolution apparatus (paddle) according to US Pharmacopeia XXII in 0.05 M phosphate buffer at pH 6.8: (a) no more than about 15% of the total fluvoxamine is released after 0.5 of an hour of measurement in the apparatus; (b) no more than

			about 25% of the total fluvoxamine is released after 1 hour of measurement in the apparatus; (c) between about 20% and 75% of the total fluvoxamine is released after 2 hours of measurement in the apparatus; (d) not less than about 75% of the total fluvoxamine is released after 4 hours of measurement in the apparatus; and (e) not less than about 85% of the total fluvoxamine is released after 6 hours of measurement in the apparatus
7438930	10/21/2008	Controlled release formulations	<p>Claim 1: wherein the formulation provides a time to mean maximum plasma concentration of methylphenidate at about 0.5 to about 4 hours after oral administration</p> <p>Claim 5: which provides a peak plasma concentration of methylphenidate which is from about 1.0 to about 2.0 times the plasma concentration of methylphenidate provided by the formulation at about 9 hours after oral administration.</p>
7410978	8/12/2008	Once daily dosage form of trospium	<p>Claim 3: provides steady state blood <math>C_{max}</math> levels of trospium in the range of about 2.5 ng/ml to about 4.5 ng/ml and <math>C_{min}</math> levels of trospium in the range of about 0.5 ng/ml to about 1.5 ng/ml.</p> <p>Claim 4: provides steady state areas under the curve (AUCs) in the range of about 30 to about 60 ng/ml*hr.</p> <p>Claim 6: provides single dose % F values in the range of about 80 to about 120.</p> <p>Claim 10: an extended release formulation that allows release of about 80% trospium chloride at 3.5 hours post ingestion</p>
7247318	7/24/2007	Oral controlled release formulation	Claim 1: wherein the formulation provides a time to maximum plasma concentration of said methylphenidate hydrochloride at about 0.5 to about 4 hours after oral administration
7108866	9/19/2006	Controlled-release Diltiazem formulation	<p>Claim 1: exhibits the following in vitro release characteristics; (i) releases the diltiazem or a pharmaceutically acceptable salt thereof into an aqueous medium at the following rates when measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900 ml of water: (a) between about 1% and about 15% after</p>

			<p>about 2 hours; (b) between about 7% and about 35% after about 4 hours; (c) between about 30% and about 58% after about 8 hours; (d) between about 55% and about 80% after about 14 hours; (e) in excess of about 75% after about 24 hours; and/or (ii) releases the diltiazem or pharmaceutically acceptable salt thereof into a buffered medium having a pH between about 5.5 and about 6.5, at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900 ml of the buffered medium: (a) between about 1% and about 25% after about 2 hours; (b) between about 7% and about 45% after about 4 hours; (c) between about 30% and about 68% after about 8 hours; (d) in excess of about 75% after about 24 hours; and further wherein said orally administrable composition having said in vitro release characteristics results in a composition that: B) when orally given to humans exhibit the following properties: (i) a higher bioavailability when given at night compared to when given in the morning without food according to FDA guidelines or criteria and (ii) bioequivalence when given in the morning with or without food according to the same FDA guidelines or criteria; and (iii) provides a Cmax of diltiazem in the blood at between about 10 hours and 15 hours after administration</p>
7094427	8/22/2006	Combination immediate release/controlled release levodopa/carbidopa dosage forms	<p>Claim 1: an immediate release component comprising a ratio of carbidopa to levodopa of from about 1:1 to about 1:50 such that the in vitro dissolution rate of the immediate release component according to measurements under the USP paddle method of 50 rpm in 900 ml aqueous buffer at pH 4 at 37°C. is from about 10% to about 99% levodopa released after 15 minutes and from about 60% to about 99% after 1 hour; and b) a controlled release component comprising a ratio of carbidopa to levodopa of from about 1:1 to about 1:50 such that the in vitro dissolution rate of the controlled release component according to measurements under the USP paddle method of 50 rpm in 900 ml aqueous buffer at pH 4 at 37°C. is from about 10% to about 60% levodopa released after 1 hour; from about 20% to about 80% levodopa released after 2 hours; and from about 30% to about 99% levodopa released after about 6 hours</p>
7083808	8/1/2006	Controlled release methylphenidate formulations	<p>Claim 1: the formulation providing a time to maximum plasma concentration at about 0.5 to about 4 hours after oral administration, a peak plasma concentration from about 3 ng/ml to about 6.5 ng/ml per 20 mg dose of methylphenidate contained in the oral dosage form, wherein the peak concentration is from about 1.0 to about 2.0 times the plasma concentration of methylphenidate provided by the formulation at about 9 hours after oral administration</p>

7074430	7/11/2006	Controlled release tramadol formulations	Claim 7: having a dissolution rate in-vitro when measured using the Ph. Eur. Paddle Method at 100 rpm in 900 ml 0.1N hydrochloric acid at 37°C. and using UV detection at 270 nm, from about 0 to about 50% tramadol released after 1 hour; from about 0 to about 75% tramadol released after 2 hours; from about 10 to about 95% tramadol released after 4 hours; from about 35 to about 100% after 8 hours; from about 55 to about 100% tramadol released after 12 hours; from about 70 to about 100% tramadol released after 16 hours; and greater than 90% tramadol released after 24 hours, by weight.
7070803	7/4/2006	Controlled release composition containing midodrine and/or desglymidodrine	<p>Claim 11: wherein the release pattern of midodrine from the composition--when tested in vitro employing an in vitro dissolution method is: 1-15% w/w is released from the composition within the first 30 min after start of the test, 10-35% w/w is released about 30 min after start of the test, 15-40% w/w is released about 1 hour after start of the test, 20-50% w/w is released about 2 hours after start of the test, 20-55% w/w is released about 3 hours after start of the test, 25-75% w/w is released about 4 hours after start of the test, 30-74% w/w is released about 6 hours after start of the test, 35-85% w/w is released about 7 hours after start of the test, 45-95% w/w is released about 8 hours after start of the test, 65-100% w/w is released about 10 hours after start of the test, and 90-110% w/w is released about 12 hours after start of the test</p> <p>Claim 12: the release pattern of midodrine from the composition--when tested in vitro employing an in vitro dissolution method is as follows (<math>\pm 30\%</math> w/w of the values stated below): about 25% w/w is released about 30 min after start of the test, about 35% w/w is released about 1 hour after start of the test, about 39% w/w is released about 2 hours after start of the test, about 47% w/w is released about 3 hours after start of the test, about 53% w/w is released about 4 hours after start of the test, about 66 w/w is released about 6 hours after start of the test, about 75% w/w is released about 7 hours after start of the test, about 80% w/w is released about 8 hours after start of the test, and about 90% w/w is released about 10 hours after start of the test, and about 100% w/w is released about 12 hours after start of the test.</p>
6770295	8/3/2004	Controlled release tolterodine formulation	<p>Claim 1: a controlled release formulation capable of maintaining a substantially constant serum level of the active moiety or moieties</p> <p>Claim 2: controlled release formulation provides a mean fluctuation index of said serum level of active moiety or moieties that is not higher than about 2.0,</p>

			said fluctuation index, FI, being defined as $FI = (C_{max} - C_{min}) / AUC_{\tau} / \tau$
6746691	6/8/2004	Intermediate release nicotinic acid compositions	Claim 1: an in vitro dissolution profile, when measured in a type I dissolution apparatus (basket), according to U.S. Pharmacopeia XXII, at about 37°C. in deionized water at about 100 rpm, as follows: (a) less than about 15% of the nicotinic acid is released after about 1 hour in the 1510 apparatus, (b) between about 15% and about 30% of the nicotinic acid is released after about 3 hours in the 1510 apparatus, (c) between about 30% and about 45% of the nicotinic acid is released after about 6 hours in the 1510 apparatus, (d) between about 40% and about 60% of the nicotinic acid is released after about 9 hours in the 1510 apparatus, (e) between about 50% and about 75% of the nicotinic acid is released after about 12 hours in the 1510 apparatus, and (f) at least about 75% is released after about 20 hours in the 1510 apparatus
6720004	4/13/2004	Controlled release formulation of divalproex sodium	Claim 1: said formulation exhibits the following in-vitro dissolution profile, when measured in a type 2 dissolution apparatus (paddle) at 100 rpm, at a temperature of $37 \pm 0.5$ C, in 500 ml of 0.1N HCl for 45 minutes, followed by 900 ml of 0.05 M phosphate buffer containing 75 mM sodium laurel sulfate (pH5.5) for the remainder of the testing period: i. from about 15% to about 27% of total valproate is released after 3 hours of measurement in said apparatus; ii. from about 44% to about 69% of total valproate is released after 9 hours of measurement in said apparatus; iii. from about 59% to about 90% of total valproate is released after 12 hours of measurement in said apparatus
6673367	1/6/2004	Controlled release methylphenidate formulations	Claim 1: to provide an in-vitro dissolution of the drug of from about 0 to about 45% released after 0.25 hour; from about 10 to about 50% released after about 1 hour; from about 30 to about 80% drug released after about 4 hours; not less than about 65% drug released after 8 hours; and not less than about 80% of the drug released after about 12 hours; the oral dosage form when orally administered to a human patient further providing a time to maximum plasma concentration at about 0.5 to about 2 hours after oral administration, and a duration of effect which lasts from about 8 to about 10 hours after oral administration, wherein the plasma concentration of the drug rapidly falls at about 8 to about 10 hours after oral administration to a level which is below the minimum effective plasma concentration
6630162	10/7/2003	Controlled	Claim 1: exhibits controlled in vitro release of the



		release tolterodine formulation	active ingredient in phosphate buffer at pH 6.8 of not less than about 80% after 18 hours and after oral administration to a patient is capable of maintaining a substantially constant serum level of the active moiety or moieties for 24 hours, and wherein the controlled release formulation provides a mean fluctuation index of said serum level of active moiety or moieties that is not higher than about 2.0, said fluctuation index, FI, being defined as $FI = (C_{max} - C_{min}) / AUC_{\tau} / \tau$
6592902	7/15/2003	Controlled release eplerenone compositions	Claim 1: wherein about 50% of said eplerenone is dissolved in vitro in at least about 1.5 hours in a 1% sodium dodecyl sulfate solution at 37°C.

Applicants respectfully submit that the multitude of patents issuing and having terms of approximation in relation to dissolution/PK parameters demonstrates that this is common practice in the field to effectively secure adequate protection around such dissolution/PK parameters for controlled release formulations and that a person skilled in this field can readily understand such claim terms. This constitutes evidence that such claim terms are not considered indefinite<sup>2</sup> and are understandable to a person of ordinary skill in this art.

#### USPTO Board Decisions

A search of decisions by the USPTO Board of Patent Appeals and Interferences finds that the Board has consistently held that claims using the term “about”, in order to provide a level of approximation and sufficient protection in a variety of technical fields and contexts, are not considered indefinite. Below is a sampling of such Board decisions. This is presented simply as additional evidence that the USPTO has, in many contexts and technical fields, already taken the position that the claim term “about” is generally acceptable and understandable to persons skilled in the art.

Case Name	Appeal No.	Appln No.	Technical Field	Decision Date
Ex parte Ware	2009-014593	11/142651	Cryopreservation technology	5/20/2010
Ex parte Yardley	2009-001146	10/689379	Papermaking	7/21/2009
Ex parte Choi	2009-003196	09/792305	Negative electrode material	7/13/2009
Ex parte Madoff	2007-3524	09/272542	Automated action system	10/21/2008
Ex parte Heck	2008-2875	10/925392	Plant genetic engineering	9/16/2008

<sup>2</sup> Claims of issued U.S. Patents are presumed valid under U.S. law, 35 USC § 282, and therefore presumed definite.

Ex parte Johnson	2002-0901	09/126996	Computer system	11/26/2003
Ex parte Banerjee	2001-0570	09/049591	Capacitor	4/7/2003

### **Court Decisions**

The Federal Circuit has found that: (1) although it is rarely feasible to attach a precise limit to “about”, the usage can usually be understood in light of the technology embodied in the invention; (2) mathematical precision should not be imposed for its own sake and a patentee has the right to claim the invention in terms that would be understood by persons skilled in the art; and (3) extrinsic evidence of meaning and usage in the art may be helpful in determining the criticality of the parameter.

See *Modine Mfg. Co. v. United States Int’l Trade Comm’n*, 75 F.3d 1545 (Fed Cir 1996), at pg 1554 (emphasis added):

The specification uses the qualifier “about,” and also states that the optimum hydraulic diameter varies with the conditions. Such broadening usages as “about” must be given reasonable scope; they must be viewed by the decisionmaker as they would be understood by persons experienced in the field of the invention. *Andrew Corp. v. Gabriel Electronics, Inc.*, 847 F.2d 819, 821-22, 6 USPQ2d 2010, 2013 (Fed.Cir.), *cert. denied*, 488 U.S. 927, 109 S.Ct. 312, 102 L.Ed.2d 330 (1988). Although it is rarely feasible to attach a precise limit to “about,” the usage can usually be understood in light of the technology embodied in the invention.

See *Modine* at pg. 1557 (emphasis added):

In this case the specification itself used the terms “relatively small,” and “about 0.015-0.040,” and the construction required to preserve the claims’ validity was simply that “relatively small” and “about 0.015-0.040” not include invalidating prior art. It was evident from the prosecution history that the patentability of claims 9 and 10 did not require an exact numerical limit of the hydraulic diameter. Mathematical precision should not be imposed for its own sake; a patentee has the right to claim the invention in terms that would be understood by persons of skill in the field of the invention.

See also *Ortho-McNeil Pharmaceutical, Inc. v. Caraco Pharmaceutical Laboratories, Ltd.*, 476 F.3d 1321 (Fed. Cir. 2007), at 1326 (emphasis added):

This court has looked at the meaning of the term "about," and similar qualifying words or phrases, in other cases and has developed an approach to the interpretation of such terms:

"[T]he word "about" does not have a universal meaning in patent claims, . . . the meaning depends upon the technological facts of the particular case.

\* \* \*

"The use of the word "about," avoids a strict numerical boundary to the specified parameter. Its range must be interpreted in its technological and stylistic context. . . . Extrinsic evidence of meaning and usage in the art may be helpful in determining the criticality of the parameter . . ."

*Pall Corp. v. Micron Separations, Inc.*, 66 F.3d 1211, 1217 (Fed.Cir.1995) (citations omitted). See also *Modine Mfg. Co. v. United States Int'l Trade Comm'n*, 75 F.3d 1545, 1554 (Fed.Cir.1996) (stating that "the usage [of the term 'about'] can usually be understood in light of the technology embodied by the invention")

For all the above reasons, Applicants respectfully submit that the weight of the evidence in this case demonstrates that persons of ordinary skill in the art would understand the claim terms of approximation as used in the context of defining dissolution/PK parameters of controlled release formulations as in the instant application, and that such terms are therefore not indefinite but are necessary in order to provide adequate protection in this field. As noted previously, this conclusion is additionally supported by the substantial extrinsic evidence of usage of such terms in this art as represented by the multitude of issued U.S. patents in this field employing such terms of approximation. Withdrawal of this rejection is therefore respectfully requested.

#### **Claim Rejections Under 35 USC § 103**

Claims 1, 3-10, 12-15, 20, 24-25 and 28-41 stand rejected under 35 USC §103 over:

- (1) Holman (US 6,277,875) in view of Pospisilik (US2002/0103240) and Vandercruys et al (WO 00/59477);
- (2) Pospisilik (US2002/0103240) in view of Vandercruys et al (WO 00/59477); and
- (3) Pospisilik (US2004/0068119) in view of Vandercruys et al (WO 00/59477).

Applicants respectfully traverse.

The pending claims are directed to a once daily sustained release composition comprising:

- (1) about 0.1 to about 10 mg of pramipexole dihydrochloride monohydrate;
- (2) about 25% to about 75% by weight starch; and
- (3) about 20% to about 70% by weight hydrophilic polymer;

and said composition exhibiting at least one of:

(a) a particular in vitro release profile – no more than about 20% pramipexole dissolved within 2 hours after placement in a standard dissolution test; and

(b) a particular in vivo release profile – time to reach a mean of 20% absorption is greater than about 2 hours and/or the time to reach a mean of 40% absorption is greater than about 4 hours;

and

(c) when administered once daily (as a full daily dose in a single dosage unit), exhibits the bioavailability substantially equivalent to an equal daily dose of a immediate release formulation administered three times a day.

Applicants respectfully submit that the combination of references cited by the Examiner does not fairly suggest or render obvious a sustained release composition having the claimed combination of components and properties as recited above.

### **No Prima Facie Case of Obviousness Established**

#### **I. No Evidentiary Basis Presented for Obviousness**

In order to establish a *prima facie* case of obviousness, there must be some rational, evidentiary basis presented supporting the argument that a person skilled in the art would have found the claimed invention obvious over the prior art. No such evidence has been presented.

It is clear that neither Holman nor Pospisilik ('240 or '119), either alone or together, disclose or in any way suggest a sustained release pramipexole composition having the specifically claimed combination of components and release properties as recited above. As set forth in detail at pages 11-14 of the last response filed May 12, 2010, herein incorporated by reference, Holman is directed to an immediate release pramipexole formulation, and Pospisilik is directed to a process for resolving pramipexole into enantiomers with only a very brief, general description of formulating sustained release dosage forms and no disclosure or suggestion of the specific combination of components or the release profile as instantly claimed.

Recognizing this deficiency, the Examiner relies heavily on Vandercruys as disclosing that starches in combination with hydrophilic polymers have been used in the art to formulate controlled release dosage forms, there being no such specific disclosure in either of the other two cited references. The Examiner further relies upon the data in Table 5 as demonstrating a specific controlled release composition achieving the in-vitro sustained release profile as instantly claimed.

However, a careful reading of Vandercruys as a whole shows that:

(1) there is a high level of unpredictability in modifying the types or amounts of ingredients in controlled release dosage forms;

(2) a slight increase in the amount of starch generally results in a significant increase in the release rate;

(3) the reference as a whole teaches away from significantly increasing the amount of starch while also maintaining the controlled release profile relied upon by the Examiner (and shown in Table 5).

As outlined at pages 14-16 of the response filed May 12, 2010, herein incorporated by reference:

(1) Table 5 relied on by the Examiner refers to data relating to Tablet 6;

(2) Tablet 6 is a controlled release formulation of a poorly soluble active that is chemically distinct from pramipexole, which is a highly soluble active, and therefore there is no basis for predicting whether such formulation would or could achieve the same sustained release profile with pramipexole. This is according to the unrebutted, evidentiary-based opinion of Applicants' formulation expert Dr. John M. Heimlich (see Heimlich Declaration at paragraphs 16-18);

(3) All the examples of controlled release tablets in Vandercruys have starch in the very narrow window of 3% to 5% by weight, with Tablet 6 having only 3% starch – the lowest amount of starch of all the tablets described and tested in this reference.

(4) The release data provided in Vandercruys shows that tablets having just slightly higher amounts of starch (5% instead of 3%) have significantly faster release rates than Tablet 6, most of them falling well outside the in vitro release parameters claimed in the instant application.

The Examiner has not presented any evidence to rebut the evidentiary-based findings outlined above.

Applicants submit that the only reasonable inference from the above findings is that: (1) there is a high level of unpredictability in this art, especially with respect to modifying the types or amounts of constituent ingredients in such controlled release formulations; and (2) the

reference as a whole would teach a person skilled in the art away from using higher amounts of starch if the desire was to maintain the controlled release profile shown for Tablet 6.

The Examiner has not provided a rational, evidentiary-supported basis for concluding that the instantly claimed sustained release pramipexole formulation – having the combination of constituent ingredients in the amounts stated and having the claimed release profile – would be obvious over the cited references. On the contrary, the un rebutted evidence in this case would indicate that the instantly claimed invention is non-obvious.

## **II. Lack of Reasonable Expectation of Success**

In order to find obviousness, there must be some reasonable expectation of success in achieving the claimed invention. Such is lacking in the present case.

As outlined in the section bridging pages 7 to 8 of the response filed 11/26/2008, incorporated herein by reference, formulation of sustained release dosage forms is a highly individualized matter depending on the overall properties of the particular drug. This concept is widely accepted, as set forth in the Ansel reference cited in the response filed 11/26/2008 (Ansel, *Introduction to Pharmaceutical Dosage Forms*). Thus, one skilled in the art would not reasonably expect two compounds with different chemical structures and properties to have similar effects in a sustained release dosage form.

Consistent with the above general principle, Applicants' pharmaceutical formulation expert Dr. Heimlich has found, and has specifically stated in his Declaration filed with the previous response, that:

(1) The active compound in Tablet 6 of Vandercruys is both chemically distinct from pramipexole and has distinct properties in being poorly soluble (whereas pramipexole is highly soluble) (see Heimlich Declaration at paragraphs 16-17);

(2) There is nothing in Vandercruys whereby one could predict whether the disclosed formulation, or one which is similar, would provide the same sustained release properties for the chemically distinct, highly soluble compound pramipexole (see Heimlich Declaration at paragraph 18); and

(3) None of the cited references suggest or provide a person skilled in the art with any reasonable expectation of success in arriving at the instantly claimed sustained release formulation of pramipexole having the sustained release profile as instantly claimed. (see Heimlich Declaration at paragraphs 5, 12, 14 and 20)

The Examiner has not provided any evidence rebutting the above findings of Applicants' expert of lack of predictability and lack of any reasonable expectation of success in arriving at the present invention.

### **III. USPTO Obviousness Guidelines and KSR**

A review of the USPTO's own obviousness guidelines implemented following the decision of *KSR International Co. v. Teleflex Inc.*, 550 U.S. 398, 82 U.S.P.Q.2d 1385 (2007) indicates that a *prima facie* case of obviousness has clearly not been established in the instant case.

Attention is directed to the following MPEP sections outlining the USPTO's obviousness guidelines (emphasis added):

#### **MPEP 2141: Examination Guidelines for Determining Obviousness Under 35 U.S.C. 103;** **Section III. RATIONALES TO SUPPORT REJECTIONS UNDER 35 U.S.C. 103:**

The key to supporting any rejection under 35 U.S.C. 103 is the clear articulation of the reason(s) why the claimed invention would have been obvious. The Supreme Court in *KSR* noted that the analysis supporting a rejection under 35 U.S.C. 103 should be made explicit. The Court quoting *In re Kahn*, 441 F.3d 977, 988, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006), stated that "[R]ejections on obviousness cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *KSR*, 550 U.S. at \_\_\_, 82 USPQ2d at 1396.

In the present case, Applicants submit that the Examiner has not provided "articulated reasoning with some rational underpinning" to support obviousness. This is especially true in light of the specific teachings of the cited references as discussed in detail above.

#### **MPEP 2141: Examination Guidelines for Determining Obviousness Under 35 U.S.C. 103;** **Section III. RATIONALES TO SUPPORT REJECTIONS UNDER 35 U.S.C. 103:**

Exemplary rationales that may support a conclusion of obviousness include:

- (A) Combining prior art elements according to known methods to yield predictable results;
- (B) Simple substitution of one known element for another to obtain predictable results;
- (C) Use of known technique to improve similar devices (methods, or products) in the same way;
- (D) Applying a known technique to a known device (method, or product) ready for improvement to yield predictable results;

(E) "Obvious to try" - choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success;

(F) Known work in one field of endeavor may prompt variations of it for use in either the same field or a different one based on design incentives or other market forces if the variations are predictable to one of ordinary skill in the art;

(G) Some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention.

Applicants respectfully submit that the Examiner has failed herein to demonstrate the existence of any of the above rationale supporting obviousness in accordance with the USPTO guidelines.

MPEP 2141.02 Differences Between Prior Art and Claimed Invention:

Section VI. PRIOR ART MUST BE CONSIDERED IN ITS ENTIRETY, INCLUDING DISCLOSURES THAT TEACH AWAY FROM THE CLAIMS:

A prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention.

Applicants respectfully submit that the Examiner has not considered the entirety of the Vandercruys reference, including the disclosures therein that Applicants submit would lead a person skilled in the art away from modifying its teachings in order to arrive at a sustained release formulation having the instantly claimed release profile, as discussed in detail above.

MPEP 2143.01 Suggestion or Motivation To Modify the References:

III. FACT THAT REFERENCES CAN BE COMBINED OR MODIFIED MAY NOT BE SUFFICIENT TO ESTABLISH *PRIMA FACIE* OBVIOUSNESS

The mere fact that references can be combined or modified does not render the resultant combination obvious unless the results would have been predictable to one of ordinary skill in the art. *KSR International Co. v. Teleflex Inc.*, 550 U.S. \_\_\_\_, \_\_\_\_, 82 USPQ2d 1385, 1396 (2007)

Again, as set forth in detail above, there is a high level of unpredictability in this field of controlled release dosage forms, as demonstrated by (1) basic literature in the field (see, e.g., *Ansel* reference); (2) the teachings and data presented in Vandercruys; and (3) the findings of Applicants' expert regarding the lack of predictability and lack of any reasonable expectation



of success in this field and, in particular, in going from the teachings of the cited references to the instantly claimed invention.

For all the above reasons, Applicants respectfully submit that no *prima facie* case of obviousness over the cited art has been established in the present case, and withdrawal of these rejections is respectfully requested.

### **Conclusion**

In view of the remarks above, Applicants respectfully submit that the pending claims are allowable, and request issuance of a notice to that effect. If a telephone interview is deemed to helpful, the Examiner is invited to contact applicants' undersigned attorney.

Respectfully submitted,

Dated: December 16, 2010

/Seth H. Jacobs/  
Seth H. Jacobs  
Reg. No. 32,140  
Phone: (212) 733-3678